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ARTICLE

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Abstract

Preliminary data suggest that allogeneic stem cell transplantation (allo-SCT) may be effective in T-prolymphocytic leukemia (T-PLL). The purpose of the present observational study was to assess the outcome of allo-SCT in patients aged 65 years or younger with a centrally confirmed diagnosis of T-PLL. Patients were consecutively registered with the EBMT at the time of transplantation and followed by routine EBMT monitoring but with an extended dataset. Between 2007 and 2012, 37 evaluable patients (median age 56 years) were accrued. Pre-treatment contained alemtuzumab in 95% of patients. Sixty-two percent were in complete remission (CR) at the time of allo-SCT. Conditioning contained total body irradiation with 6 Gy or more (TBI6) in 30% of patients. With a median follow-up of 50 months, the 4-year non-relapse mortality, relapse incidence, progression-free (PFS) and overall survival were 32, 38, 30 and 42%, respectively. By univariate analysis, TBI6 in the conditioning was the only significant predictor for a low relapse risk, and an interval between diagnosis and allo-SCT of more than 12 months was associated with a lower NRM. This study confirms for the first time prospectively that allo-SCT can provide long-term disease control in a sizable albeit limited proportion of patients with T-PLL.

Introduction

T-prolymphocytic leukemia (T-PLL) is a rare neoplasm belonging to the mature T-cell lymphomas according to the WHO classification. The disease has usually an aggressive course with a median survival of less than one year with standard chemotherapy. A major therapeutic improvement was achieved following the introduction of alemtuzumab, which results in overall response rates in >90% of patients, including a high proportion of complete responses (CR) when given intravenously first-line as single agent or as part of a chemoimmunotherapy program [1–3]. These responses were, however, associated with limited duration and the prognosis remained rapidly fatal, prompting investigators to explore allogeneic stem cell transplantation (allo-SCT) in T-PLL.

Initial analyses of the use of allo-SCT in T-PLL suggested that a long-term disease control might indeed be possible in a proportion of patients as indicated by 3-year progression-free survival (PFS) rates between 20 and 30% [4–7]. However, all these studies are retrospective, included mostly transplants performed before 2005 and were limited by considerable heterogeneity in terms of patient baseline characteristics and transplant strategies.

The purpose of the present observational study was to prospectively follow patients with a centrally confirmed diagnosis of T-PLL who underwent an allo-SCT from an HLA-identical donor in a non-progressive disease status and were registered with the EBMT at the time of transplant. Given the notion that without transplantation, all patients with T-PLL responding to first-line therapy will inevitably relapse, usually after a short remission duration, and are difficult to salvage [8], first-line transplants have been increasingly used in recent years.

Supplementary information The online version of this article (https://doi.org/10.1038/s41409-019-0448-x) contains supplementary material, which is available to authorized users.

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Patients and Methods

Data source

EBMT is a voluntary organization comprising more than 500 transplant centers mainly from Europe. Accreditation as a member center requires submission of minimal essential data (MED-A form) from all consecutive patients to a central registry in which patients may be identified by the diagnosis of the underlying disease and type of transplantation. All transplant centers have to obtain written informed consent prior to data registration with the EBMT following the Helsinki Declaration 1975. Individual IRB approvals were obtained at the participating center level where appropriate.

Study design

Eligible for this registry-based prospective observational study were all the consecutive patients aged 18–65 years who underwent a planned allo-SCT from an HLA-identical related or unrelated donor for non-progressive T-PLL at the participating 25 EBMT centers. Baseline patients' and disease characteristics were submitted along with the registration for the study at the time of admission for allo-SCT. Details on pre-transplantation treatment and transplantation were collected subsequently according to EBMT procedures. In addition, submission of a written diagnostic histopathology and/or immunophenotyping report confirmatory for a diagnosis of T-PLL was mandatory for inclusion in the study. The full protocol of the study including the diagnostic criteria applied can be found in the supplemental Appendix (online only). Accrual target was 50 patients.

Statistical analysis

The primary endpoint was non-relapse mortality (NRM), defined as death in the absence of relapse or progression since allo-SCT. Secondary endpoints were overall survival (OS), PFS and incidence of disease relapse or progression (RI). Additional endpoints were grade II–IV and III–IV acute graft-versus-host disease (GVHD), and limited and extensive chronic GVHD. OS was defined as the time from allo-SCT to death from any cause and PFS was defined as the time from allo-SCT to relapse or progressive disease or death from any cause, whichever came first. The probabilities for OS and PFS were estimated from the time of allo-SCT using the Kaplan–Meier product-limit estimator and differences in subgroups were assessed by the log-rank test. The median follow-up was calculated using the reverse Kaplan–Meier estimator. Estimates of NRM and RI were calculated using cumulative incidence rates to accommodate competing risks and were compared by Gray's test. Each of the primary and secondary endpoints were evaluated at 48 months. Acute and chronic GVHD were estimated as the cumulative incidence of grade II–IV and III–IV acute GVHD, and limited and extensive chronic GVHD respectively, with death from any cause as the competing event. Acute GVHD was evaluated at 100 days, and both forms of chronic GVHD were evaluated at 12 months. The impact of chronic GVHD on outcome was analyzed by means of a Cox model in which the occurrence of chronic GVHD was included as a time-dependent covariate. Because of the small number of events, only univariate analyses were performed. P-values <0.05 were considered significant. All estimates are reported with accompanying 95% confidence intervals in brackets. All analyses were performed in R version 3.2.2. using packages 'survival', 'prodlim' and 'cmprsk'.

Results

Study population

Between January 2007 and May 2012, 54 patients from 25 European centers were registered for this study. Of these, 4 patients were excluded because the written diagnostic reports were considered as not confirmative for a diagnosis of T-PLL after central review (T-lymphoblastic leukemia/lymphoma – 2, aggressive NK-cell leukemia – 2). Another 11 patients did not meet baseline eligibility because they were older than 65 years [4], had progressive disease at allo-SCT [2], or were allografted with cord blood [3] or a mismatched unrelated donor [2]. For 2 additional patients, follow-up data beyond registration information was not provided, leaving 37 patients evaluable for study endpoints.

Patients' characteristics

Patients' characteristics and transplant strategies are summarized in Table 1. There was a male predominance and the median age was 56 years at transplant. The majority of patients had received the allo-SCT in first CR or partial remission (PR); 65% of the patients underwent the transplant within the first year after diagnosis and 92% within 2 years. Only the 2 patients who had undergone an autologous SCT as part of the first-line strategy had a substantially longer time interval from diagnosis to allotransplant of 42 and 48 months, respectively. Almost all patients had been exposed to alemtuzumab prior to transplantation with a median time interval between the last alemtuzumab dose and the allo-SCT of 75 days (interquartile range 53–152). Alemtuzumab was administered either as monotherapy or in combination with different

chemotherapy regimens, mostly fludarabine-based or CHOP. Conditioning intensity was considered as myeloablative by the Working group criteria [9] in 35% of the patients. Total body irradiation (TBI) of doses of 6 Gy or higher were administered to 30% of patients.

Outcome

Except for a single patient with early death, all patients engrafted. Acute GvHD grade II–IV before day 100 was reported in 19% (6–32%) of patients and acute GvHD grade III–IV in 11% (1–21%). The cumulative incidence of overall and extensive chronic GVHD at 12 months post allo-SCT was 43% (27–59%) and 21% (7–35%), respectively.

Twelve patients died of NRM at a median time of 6 (0.5–74) months after allo-SCT, corresponding to NRM incidences of 25% (11–39%) and 32% (16–47%) at 2 and 4 years, respectively. T-PLL recurrence was reported in 13 patients, with only 2 relapses occurring beyond 24 months post-transplantation, translating into a 4-year RI of 38% (22–55%). With a median follow-up of surviving patients of 50 months (range 12–78), the 4-year OS and PFS were 42% (25–59%) and 30% (14–46%), while the median OS and PFS was 27.8 and 19.2 (11.6–46.7) months, respectively (Fig. 1).

Prognostic factors

By univariate analysis taking into account age, gender, time from diagnosis to first treatment, time from first treatment to transplantation, time from diagnosis to transplantation, interval between alemtuzumab withdrawal and allo-SCT, type of previous treatment (alemtuzumab monotherapy versus chemoimmunotherapy versus chemotherapy only), disease status at transplantation, type of donor, TBI >6Gy in the conditioning and conditioning intensity, significant predictors of a favorable outcome were an interval from diagnosis to allo-SCT >12 months (for NRM) and use of a conditioning regimen containing TBI dosed with 6Gy or more (for RI) (Table 2). The 4-year PFS of patients in CR at transplant was 41 (19–61) vs 15% (0–35), which did not reach statistical significance. There was no impact of chronic GVHD, analyzed as a time-dependent covariate, on both relapse incidence and survival, the HRs being 0.81 (0.25–2.64), $p = 0.73$ and 0.94 (0.33–2.7), $p = 0.908$.

Discussion

This observational study aimed at prospectively investigating the outcome of allo-SCT in consecutive T-PLL patients fulfilling well-defined baseline characteristics (age

Table 1 Patients' characteristics and transplant strategies in T-PLL, separately for all patients and patients who received at least 6Gy TBI or less than 6Gy TBI

Variable	All patients	TBI < 6Gy	TBI > =6Gy
Number of patients	37	26	11
Age at transplantation (years; median, IQR)	56 (47–59)	56 (49–59)	56 (44–59)
Gender male	27 (73%)	20 (77%)	7 (64%)
Interval from diagnosis to 1st treatment line < = 3 months	25 (69%)[a]	16 (64%)	9 (82%)
Interval from 1st treatment line to allo-SCT < = 12 months	31 (86%)[a]	21 (84%)	10 (91%)
Interval from diagnosis to allo-SCT < = 12 months	24 (65%)	15 (58%)	9 (82%)
Months from diagnosis to allo-SCT (median, IQR)	8 (6–17)	11 (6–18)	6 (5–7)
Number of treatment lines prior to allo-SCT			
1	26 (72%)	18 (72%)	8 (73%)
2	8 (22%)	5 (20%)	3 (27%)
>2	2 (6%)[a]	2 (8%)	0 (0%)
First-line alemtuzumab -> intent-to-first- line allo-SCT strategy pursued, thereof	28 (80%)	19 (73%)	9 (82%)
Alemtuzumab monotherapy	18 (51%)	14 (54%)	4 (36%)
Chemoimmunotherapy	10 (29%)[b]	5 (19%)	5 (45%)
Previous alemtuzumab (in any line)	35 (95%)	24 (92%)	11 (100%)
Days between the last alemtuzumab dose and allo-SCT (median, IQR)[c]	75 (53–152)	85 (61–152)	61 (50–70)
Performance status at transplantation (Karnofsky)			
90–100	24 (69%)	16 (67%)	8 (73%)
70–80	11 (31%)[b]	8 (33%)	3 (27%)
Disease status at transplantation			
CR 1	16 (44%)	12 (67%)	4 (36%)
CR>1	6 (17%)	3 (12%)	3 (27%)
PR 1	8 (22%)	5 (20%)	3 (27%)
PR>1	1 (3%)	1 (4%)	0 (0%)
PR or CR>1	1 (3%)	1 (4%)	0 (0%)
SD	4 (11%)[a]	3 (12%)	1 (9%)
Conditioning			
Myeloablative	13 (35%)	6 (23%)	7 (64%)
Reduced-intensity	24 (65%)	20 (77%)	4 (36%)
Conditioning (TBI-based)			
Myeloablative	7 (19%)	0 (0%)	7 (64%)
Reduced-intensity	6 (16%)	2 (100%)	4 (36%)
TBI			
2Gy	2 (5%)	2 (100%)	0 (0%)
6Gy	4 (11%)		4 (36%)

Table 1 (continued)

Variable	All patients	TBI < 6Gy	TBI > =6Gy
8Gy	1 (3%)		1 (9%)
12Gy	4 (11%)		4 (36%)
13Gy	1 (3%)		1 (9%)
14.4Gy	1 (3%)		1 (9%)
T-cell depletion			
No	17 (46%)	11 (42%)	6 (55%)
In vivo	19 (51%)	14 (54%)	5 (46%)
ATG	13 (35%)	9 (35%)	4 (36%)
Alemtuzumab	6 (16%)	5 (19%)	1 (10%)
Ex vivo	1 (3%)	1 (4%)	0 (0%)
Donor type			
Matched related	15 (43%)	11 (42%)	4 (36%)
Matched unrelated	22 (57%)	15 (58%)	7 (64%)
Source of stem cells			
Peripheral blood	36 (97%)	26 (100%)	10 (91%)
Bone marrow	1 (3%)	0 (0%)	1 (9%)
GvHD prophylaxis			
Cyclosporine and methotrexate	17 (46%)	10 (38%)	7 (64%)
Cyclosporine and MMF	8 (22%)	8 (31%)	0 (0%)
Methotrexate alone	2 (5%)	1 (4%)	1 (9%)
MMF alone	2 (5%)	2 (8%)	0 (0%)
Cyclosporine alone	6 (16%)	5 (19%)	1 (9%)
Other	2 (5%)	0 (0%)	2 (18%)

[a]Data available for 36 patients

[b]Data available for 35 patients

[c]Data available for 27 patients

<65, good performance status, sensitive disease, well-matched donor) in registered EBMT centers, thereby avoiding the selection bias and heterogeneity inherent to the few retrospective case series [4–7], which represent the only source of information on allo-SCT in T-PLL available to date. Focusing on patients with a favorable disease and transplant risk, the outcome in this study with 4-year OS and PFS estimates of 42 and 30%, respectively, tends to be superior to what has been observed in the retrospective registry studies mentioned, though the improvement does not seem to be substantial.

Almost all of our patients had been pre-treated with alemtuzumab prior to transplant, most of them following an intent-to-transplant-in-CR1 strategy. This resulted only in a modest outcome improvement in the patients actually transplanted as captured by this study, if any. Nevertheless, it might well have been that this approach has resulted in a higher proportion of patients achieving CR (and thus optimum transplant eligibility) than with chemotherapy alone. Notably, we did not observe an adverse effect of the time interval between alemtuzumab withdrawal and allo-SCT on

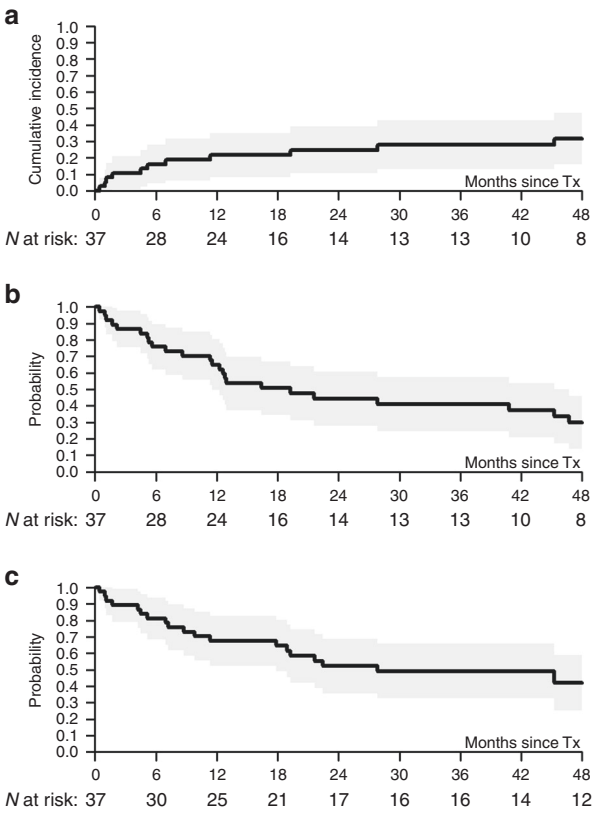

Fig. 1 Non-relapse mortality (**a**), progression-free survival (**b**), and overall survival (**c**) of all 37 patients

post-transplant disease control, suggesting that outcome was not heavily affected by in-vivo T-cell depletion caused by alemtuzumab serum levels persisting beyond the date of transplant. There was also no relation between the time interval between alemtuzumab withdrawal and allo-SCT in terms of non-relapse mortality and acute GVHD occurrence.

However, both NRM and long-term disease control provided by allo-SCT even if performed in profound CR are still unsatisfactory. Therefore, the development of novel additional therapeutic tools for targeting residual T-PLL causing post-transplant relapse is eagerly awaited. (Alemtuzumab is unsuitable for this purpose since it strongly counteracts any graft-versus-leukemia (GVL) activity and has no durable effect per se in T-PLL [8].) Whether new agents such as venetoclax [10], anti-HDAC inhibitors e.g. romidepsin (NCT02512497), JAK/STAT pathway inhibitors [11] or PARP inhibitors [12] will be helpful in maintenance or preemptive treatment after allo-SCT is a matter of future studies. As long as such agents are unavailable, bridging the time gap until GVL becomes effective relies essentially on the conditioning regimen. To this end, we did not find a significant impact of conditioning intensity on post-transplant disease control, but notably those patients who had received TBI dosed 6 Gy or higher had a significantly lower relapse risk by univariate analysis than

Table 2 Univariate prognostic factor analysis with 4-year estimates of proportions

		OS	*p* value	PFS	*p* value	Relapse	*p* value	NRM	*p* value
Disease status at transplantation	No CR	31% (6–56%)	0.208	15% (0–35%)	0.098	38% (12–65%)	0.966	46% (19–73%)	0.098
	CR	52% (29–74%)		41% (18–64%)		42% (19–64%)	17% (2–33%)		
Interval from diagnosis to 1st treatment line	<=3 months	28% (9–47%)	0.059	28% (9–47%)	0.623	34% (15–54%)	0.541	38% (18–58%)	0.347
	>3 months	70% (41–99%)		25% (0–55%)		53% (20–86%)	22% (0–49%)		
Interval from 1st treatment line to allo-SCT	<=12 months	42% (24–60%)	0.847	27% (10–45%)	0.479	35% (17–53%)	0.332	38% (20–56%)	0.1
	>12 months	44% (1–88%)		44% (1–88%)		56% (12–99%)	0% (0–0%)		
Interval from diagnosis to allo-SCT	<=12 months	30% (10–49%)	0.053	25% (6–44%)	0.189	26% (8–44%)	0.107	49% (27–70%)	0.005
	>12 months	67% (41–94%)		40% (10–69%)		60% (31–90%)	0% (0–0%)		
Conditioning	Reduced-intensity	45% (23–66%)	0.796	26% (6–46%)	0.5	54% (31–76%)	0.068	21% (5–37%)	0.231
	Myeloablative	37% (10–64%)		37% (10–64%)		15% (0–35%)	48% (20–76%)		
Sex	Female	67% (35–98%)	0.091	56% (23–89%)	0.084	34% (2–66%)	0.684	10% (0–29%)	0.136
	Male	33% (14–52%)		20% (4–37%)		40% (21–59%)	40% (20–59%)		
Interval from the last alemtuzumab dose to allo-SCT	<=60 days	50% (15–85%)	0.511	25% (0–55%)	0.942	50% (15–85%)	0.699	25% (0–55%)	0.829
	>60 days	37% (13–60%)		31% (9–54%)		42% (18–66%)	26% (7–46%)		
Age	<=55	45% (21–70%)	0.855	39% (15–63%)	0.47	37% (13–60%)	0.98	24% (3–45%)	0.413
	>55	39% (15–63%)		18% (0–39%)		45% (19–70%)	37% (15–59%)		
Donor	Matched related	64% (38–90%)	0.062	39% (11–67%)	0.224	38% (11–65%)	0.933	23% (0–47%)	0.301
	Matched unrelated	29% (9–48%)		24% (5–43%)		39% (17–60%)	37% (17–58%)		
Pretreatment	Alemtuzumab monotherapy	44% (20–69%)	0.31	25% (2–48%)	0.651	51% (26–77%)	0.518	24% (3–44%)	0.164
	Alemtuzumab chemoimmunotherapy	40% (10–70%)		30% (2–58%)		40% (10–70%)	30% (2–58%)		
	Chemotherapy only	29% (0–62%)		29% (0–62%)		14% (0–40%)	57% (20–94%)		
TBI	<6Gy (including no)	39% (20–59%)	0.401	23% (6–40%)	0.112	50% (30–70%)	0.048	28% (10–45%)	0.716
	>=6Gy	47% (12–81%)		47% (12–81%)		9% (0–26%)	44% (10–78%)		

those patients whose conditioning regimen was based on low-dose TBI or chemotherapy only. The importance of TBI is in keeping with preliminary findings from our previous study [6] and suggests that TBI ≥ 6 Gy may be the preferred conditioning backbone for patients with T-PLL as long as no contrary evidence becomes available. Intermediate-dose TBI conditioning can be safely applied also in elderly patients who represent the bulk of the T-PLL target population [13]. However, since the event number was too low for a robust multivariate analysis and the sample size still small, a definite conclusion of the superiority of intermediate-dose TBI over alternative conditioning regimens cannot be drawn. Even if further studies on this issue are needed, it still seems to be reasonable to prefer intermediate-dose TBI, where it is available. In contrast to our previous study, a short interval between diagnosis and allo-SCT was not associated with a favorable outcome, but with an increased NRM risk. One explanation for this discrepancy might be the fact that unlike in the current study, in the previous EBMT series containing transplants largely performed in the pre-alemtuzumab era, many chemotherapy-refractory patients may have undergone lengthy remission induction attempts before proceeding to allo-SCT [6]. No other prognostic factors for post allo-SCT outcome have been identified so far [4, 5, 7].

Apart from TBI, the only other susceptible variable affecting outcome – though not reaching statistical significance – was being in CR at the time of transplant, again highlighting the need for novel therapeutic tools effectively targeting T-PLL. In contrast, the number of pre-treatment regimens did not affect outcome as long as a CR was present at the time of allo-SCT. However, since a second CR might be very difficult to achieve in T-PLL once disease has recurred after a first CR [8], the obvious conclusion from this finding is that eligible patients should proceed to transplant as soon as the first remission is reached if an allo-SCT is considered at all.

As in most other indications, the efficacy of allo-SCT in T-PLL basically relies on the existence of GVL activity in this disease. Although a clear plateau did not emerge, only 2 relapses occurred beyond two years post-transplant, pointing to a protracted GVL effect in the long-term survivors similar to the observations made in the retrospective series. However, it has to be kept in mind that long-term PFS has been observed also in anecdotal T-PLL cases after autoHCT [4]. Anyway GVL efficacy seems to be less effective in T-PLL than in other lymphoid malignancies, such as chronic lymphocytic leukemia (CLL) [14]. This hypothesis is based on the generally poorer long-term outcome of allo-SCT for T-PLL compared to CLL, and also on recent data on minimal residual disease kinetics related to immune-modulating events in T-PLL [15].

In keeping with this, the results of the present study were disappointing, taking into account that it was focusing on early transplantation in patients with sensitive disease. This raises the question if early allo-SCT consolidation is the way to go in T-PLL. A recent case series from the MD Anderson Cancer Center did not find an outcome advantage for 16 patients undergoing allo-SCT in CR1 compared to 26 patients without CR1 transplant consolidation [16]. The reason was that unlike in the current and the other larger published studies [4–7], long-term remissions after allo-SCT were not observed in the MD Anderson series. This might be due to the fact that the study covered a long period of 27 years, whereas our analysis is restricted to the most recent period of time.

The limitations of this study consist in the relatively small sample size and in the heterogeneity of the transplant strategies pursued. In addition, although participating centres pledged themselves to enroll all eligible patients it cannot be excluded that patients erroneously got lost because site monitoring was not performed. Nevertheless, it is the first study prospectively following consecutive patients meeting defined eligibility criteria from the time of allo-SCT. Moreover, it is the first T-PLL transplant study employing central review of diagnostic reports for validating the diagnosis of T-PLL.

In conclusion, this study confirms for the first time prospectively that allo-SCT is the only modality, which can provide long-term disease control in a sizable fraction of patients with T-PLL. In transplant-eligible patients, allo-SCT should be pursued as soon as a CR is achieved, and using intermediate/high-dose TBI seems to be recommendable. Novel therapeutic tools are needed to improve the outcome of allo-SCT and the prognosis of T-PLL patients in general; first suggestions regarding targeted therapy are coming from high-throughput studies [17].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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